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Original article

Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial

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ABSTRACT

Background: Coronavirus disease 2019 (Covid-19) has resulted in a global outbreak. Few existing targeted medications are available. Lianhuaqingwen (LH) capsule, a repurposed marketed Chinese herb product, has been proven effective for influenza.

Purpose: To determine the safety and efficacy of LH capsule in patients with Covid-19.

Methods: We did a prospective multicenter open-label randomized controlled trial on LH capsule in confirmed cases with Covid-19. Patients were randomized to receive usual treatment alone or in combination with LH capsules (4 capsules, thrice daily) for 14 days. The primary endpoint was the rate of symptom (fever, fatigue, coughing) recovery.

Results: We included 284 patients (142 each in treatment and control group) in the full-analysis set. The recovery rate was significantly higher in treatment group as compared with control group (91.5% *vs.* 82.4%, $p = 0.022$). The median time to symptom recovery was markedly shorter in treatment group (median: 7 *vs.* 10 days, $p < 0.001$). Time to recovery of fever (2 *vs.* 3 days), fatigue (3 *vs.* 6 days) and coughing (7 *vs.* 10 days) was also significantly shorter in treatment group (all $p < 0.001$). The rate of improvement in chest computed tomographic manifestations (83.8% *vs.* 64.1%, $p < 0.001$) and clinical cure (78.9% *vs.* 66.2%, $p = 0.017$) was also higher in

Abbreviations: Covid-19, coronavirus disease 2019; CT, computed tomography; 95%CI, 95% confidence interval; FAS, full-analysis set; HR, hazards ratio; LH, Lianhuaqingwen; MERS, middle east respiratory syndrome coronavirus; PV, protocol deviation; PPS, per protocol set; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Trial Registration: Chinese Clinical Trial Registry (www.chictr.org/cn/, No. Chi CTR-TRC-2000029434)

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treatment group. However, both groups did not differ in the rate of conversion to severe cases or viral assay findings (both $p > 0.05$). No serious adverse events were reported.
Conclusion: In light of the safety and effectiveness profiles, LH capsules could be considered to ameliorate clinical symptoms of Covid-19.

Introduction

Since the initial epidemics in Wuhan city, China, coronavirus disease 2019 (Covid-19) has rapidly spread globally, with 84,237 and 2,314,621 laboratory-confirmed cases in China and throughout the world as of April 21st, 2020, respectively. The number of cases might have been underestimated, possibly because asymptomatic viral carriers and patients with mild diseases have insidious or atypical symptoms and signs (WHO Collaborating Centre For Infectious Disease Modelling, 2020). The rapid outbreak worldwide could be reflected by the basic reproductive number that reached to 2.68 (Wu et al., 2020). Covid-19 is caused by the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which potently elicits pulmonary inflammation and infiltration, as well as systemic inflammatory cytokine storms. Timely treatment is cardinal to the management of Covid-19, the adverse impacts of which has been estimated to be significantly greater than those of severe acute respiratory syndrome (Yang et al., 2020).

Currently, supportive therapies are the cornerstone for the management of Covid-19. Development of a novel class of medication would not be practical within a short span during the public emergency event such as Covid-19. In light of the long history of evolution and the proven efficacy in patients with influenza (Duan et al., 2011), the traditional Chinese medicine has recently been repurposed for the clinical management of Covid-19 (Xia et al., 2020). Several candidates with possible antiviral effects have been explored (Wang et al., 2020). In the latest publication, Lianhuaqingwen (LH) capsule (Shijiazhuang Yiling Pharmaceutical Co. Ltd., Shijiazhuang, China) was a manufactured product of the traditional Chinese medicine formula marketed in China that could significantly inhibit SARS-CoV-2 replication, alter the viral morphology and confer anti-inflammatory activity *in vitro* (Li et al., 2020). Moreover, LH capsules could significantly ameliorate the cardinal symptoms (i.e., fever, cough, fatigue) and shorten the course of Covid-19 (Cheng and Li, 2020; Lu et al., 2020). According to the *Diagnosis and Treatment Protocol for Coronavirus Pneumonia (Trial version 7)* (*Diagnosis and Treatment Protocol for Coronavirus Pneumonia.* 2020), LH capsule has been endorsed by the National Health Commission for the treatment of Covid-19. However, no existing study has been conducted with a sufficient sample size and prospective randomized designs in multicenter settings.

We hypothesized that LH capsules could effectively ameliorate symptoms (including fever, cough and fatigue) and shorten the duration of viral shedding. On the basis of usual treatment, we sought to explore the safety and efficacy of LH capsules in patients with Covid-19 by conducting a multicenter randomized controlled trial in mainland China.

Methods

Study oversight

In this prospective, open-label, randomized controlled trial, we recruited patients with Covid-19 from 23 hospitals in nine provinces throughout mainland China. The study protocol has been approved by the ethics committee of each participating site. The protocol was designed based on the *Good Clinical Practice* guidelines and *The Declaration of Helsinki*, and has been registered with China Clinical Trial Registry website (www.chictr.org/cn/, No.: Chi CTR-TRC-2000029434). All patients signed written informed consent.

Patients

We recruited 284 patients with Covid-19 between February 2nd and February 15th, 2020 (**Figure 1**). Eligibility criteria consisted of the following: 1) Laboratory-confirmed cases with Covid-19 according to the *Protocol for Diagnosis and Treatment of Novel Coronarvirus Pneumonia (4th edition)* which was issued by the National Health Commission (General Office Of The National Health And Health Commission, 2020) (**Panel 1**) Being symptomatic (either having fever, coughing, or fatigue) plus radiologic abnormalities consistent with pneumonia; 3) Patients aged 18 years or greater of either sex.

Key exclusion criteria included: 1) respiratory tract bacterial infections due to primary or secondary immunodeficiency, congenital respiratory malformation, congenital heart disease, gastroesophageal reflux, and lung malformation; 2) asthma or other chronic airway diseases needing maintenance therapy, acute respiratory tract bacterial infection (i.e., bronchiectasis, tonsillitis, bronchitis, rhinosinusitis, otitis media), severe pulmonary interstitial diseases; 3) severe pneumonia needing mechanical ventilation; 4) severe systemic diseases (i.e., malignancy, autoimmune diseases, liver or renal diseases) or surgeries (splenectomy, organ transplantation) that in the judgement of the investigators could affect the assessment of efficacy; 5) women during pregnancy or lactation; 6) participation in clinical trials within 3 months; 7) known allergies to the investigational medications; 8) other conditions judged by the investigators. See the study protocol in *Online Supplement* for the withdrawal criteria.

Study medications

The major ingredients of LH consisted of *Forsythia suspensa, Lonicera japonica, Ephedra sinica, Isatis indigotica, Pogostemon cablin, Rheum palmatum, Glycyrrhiza uralensis, Dryopteris crassirhizoma, Rhodiola crenulata, Houttuynia cordata, Prunus sibirica*, gypsum and 1-menthol (see Online Supplement text for details). LH capsules were manufactured based on *The Pharmacopedia of People's Republic of China*. LH capsules were provided by the manufacturer, supplied to the participating sites, and dispensed by the designated research nurses after randomization. The routine treatment of the two groups was determined based on the *Diagnosis and Treatment Protocol for Coronavirus Pneumonia (Trial version 7)* (Diagnosis and Treatment Protocol for Coronavirus Pneumonia. 2020), at the discretion of the attending clinicians (General Office Of The National Health And Health Commission, 2020). Routine treatment generally consisted of the supportive treatment such as oxygen therapy, antiviral medications and symptomatic therapies.

Randomization

An open-label study was conducted because of the urgency of major public health events. Randomization numbers were generated using SAS statistical software package (SAS Inc., Cary, USA). A computer-generated 1:1 block randomization scheme was used to assign patients to either treatment group or control group. Each consecutively coded patient was randomly enrolled by the sub-site investigators until the total number of cases allocated to the site was reached. Competitive recruitment was adopted for enrollment.

Procedures

Eligible patients were randomized to receive usual treatment alone

based on *The Protocol for Diagnosis and Treatment of Novel Coronarvirus Pneumonia (4th edition)* (control group) or the combination of LH capsules (4 capsules thrice daily for 14 days). Adherence to the study medications, clinical outcomes, the use of concomitant medications and adverse events were recorded. Vital signs, laboratory testing, chest computed tomography and nucleic acid assays of SARS-CoV-2 were evaluated at baseline after randomization and on day 14.

In our study, symptom recovery denoted a complete remission of at least one major symptom (coughing, fever, or fatigue). An experienced radiologist who was blinded to the study allocation reviewed the chest computed tomography (CT) images from all patients. An improvement in chest CT images was defined as a decreased area of infiltration, a decreased area of any radiologic abnormality, or decreased density of the ground-glass opacity or nodules. We defined clinical cure as having met all of the following criteria: recovery of body temperature for more than 3 days, symptom recovery, marked improvement in chest CT images, and two consecutive negative SARS-CoV-2 RNA testing (at least one day apart).

Study endpoints

The primary endpoint was the rate of symptom (fever, fatigue, and coughing) recovery. Fever denoted the subaxillary temperature being 37.3 degrees or greater. The magnitude of fatigue and coughing was self-reported by the patients. Recovery of symptoms was defined as the complete resolution of fever, fatigue and coughing.

Secondary endpoints consisted of the time to symptom recovery, the rate of and the time to the recovery of individual symptoms, the proportion of patients with improvement on chest computed tomography, the proportion of patients with clinical cure, the timing and rate of conversion of SARS-CoV-2 RNA assay.

Safety monitoring

No major reports of the adverse events of LH capsules have been documented after marketing (Cai et al., 2012). In this study, we recorded the timing, severity, duration, measures and consequence of adverse events, and determined the association with the use of study medications.

Statistical analysis

Assuming the length of hospital stay for 14 days, and the rate of recovery of clinical symptoms (fever, fatigue, or coughing) in the control group and treatment group of 82% and 94%, we estimated a total of 240 cases (120 cases in each group) after taking into account the drop-out rate of 10% or lower.

All statistical analyses were conducted with SAS®9.4 software (SAS Institute, Cary, North Carolina). All patients were included in the full-analysis set (FAS) after randomization, while patients with major protocol deviation (PV) were removed from per protocol set (PPS). All statistical testing was two-sided, with $p < 0.05$ being considered statistically significant. Count (percentage) was adopted for summarizing the categorical variables, and compared with Chi-square tests. Continuous variables were presented with mean ± standard deviation, and compared with independent t-test or Wilcoxon rank-sum test. The time to events was presented as the median duration and 95% confidence interval (95%CI), and analyzed with Kaplan-Meier analysis. The hazards ratio (HR) of the events (i.e. symptom recovery) was also demonstrated.

Results

Patient characteristics

Of the 480 patients who were assessed for eligibility, 196 were

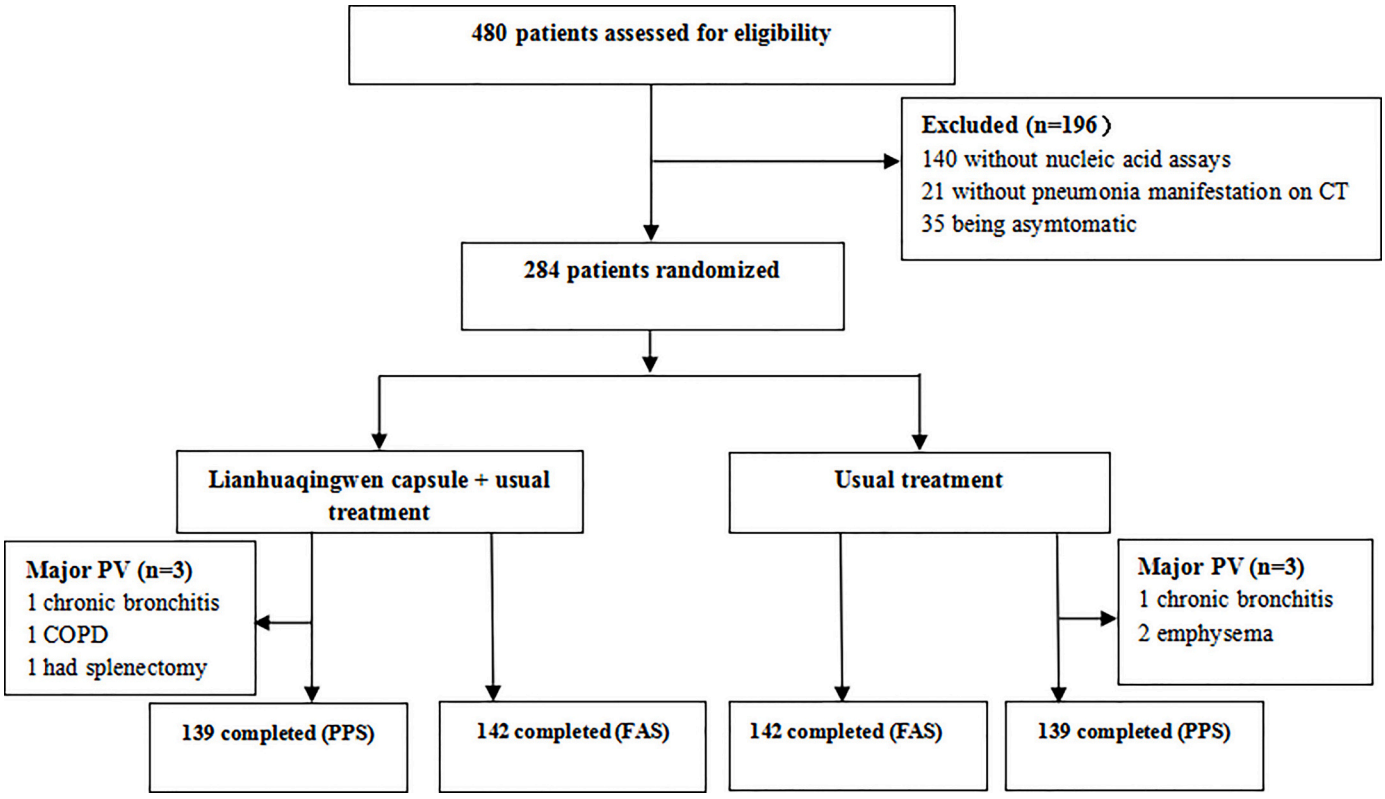

Fig. 1. Study flow chart.
PV: protocol violation; FAS: full analysis set; PPS: per protocol set.

excluded due to the lack of symptoms (not having fever, fatigue or coughing), SARS-CoV-2 assay findings, or radiologic abnormality on chest CT. Therefore, 284 patients were included in the FAS (142 each in treatment and control group). Three patients in each group had a major PV and were therefore excluded from the PPS. The treatment group had a good compliance with the study medication, with the average duration being 14.0 days (95%CI: 12.0 ~ 15.0). The study flow chart is shown in Fig. 1.

At baseline, most patients were aged above 45 years and males accounted for approximately half of the patients. More than 40% of patients had a recent of contact with people from Wuhan city. Both groups were comparable in terms of the demographic characteristics, vital signs, symptoms and concomitant treatment. 85.2% of patients each in the treatment and control group received antiviral medications such as oseltamivir ($p > 0.05$, Table 1).

Primary endpoints

The rate of symptom recovery at day 14 was significantly higher in treatment group as compared with control group (FAS: 91.5% *vs*. 82.4%, mean difference: 9.2%, 95%CI: 1.3% ~ 17.1%; PPS: 91.4% *vs*. 82.0%, mean difference: 9.4%, 95%CI: 1.3% ~ 17.4%, both $p = 0.022$) (**Fig. 2-A**).

Secondary endpoints

A significantly shorter median time to symptom recovery was observed in treatment group as compared with control group (FAS: 7 days *vs*. 10 days, HR: 1.72, 95%CI: 1.33 ~ 2.22; PPS: 7 days *vs*. 10 days, HR: 1.70, 95%CI: 1.32 ~ 2.21; both $p < 0.01$) (**Fig. 2-B, Fig. 3**). Moreover, the treatment group yielded a significantly shorter time to the recovery of fever (FAS: 2 days *vs*. 3 days, HR: 1.39, 95%CI: 1.00 ~ 1.94, $p = 0.017$; PPS: 2 days *vs*. 3 days, HR=1.46, 95%CI: 1.04 ~ 2.05, $p = 0.007$), fatigue (FAS: 3 days *vs*. 6 days, HR: 1.78, 95%CI: 1.26~2.54; PPS: 3 days *vs*. 6 days, HR: 1.72, 95%CI: 1.21 ~ 2.45; both $p < 0.001$) and coughing (FAS: 7 days *vs*. 10 days, HR: 1.71, 95%CI: 1.30~2.23; PPS: 7 days *vs*. 10 days, HR: 1.66, 95%CI: 1.27~2.18; both $p < 0.001$) (Fig. 4).

The overall rate of clinical cure was significantly higher in the treatment group as compared with control group in FAS (78.9% *vs*. 66.2%, mean difference: 12.7%, 95%CI: 2.3%22.7%, $p < 0.05$), and PPS (79.1% *vs*. 66.9%, mean difference: 12.2%. 95%CI: 1.8%22.3%, both $p = 0.022$) (Fig. 5). The rate of recovery of chest CT manifestations was also markedly higher in treatment group as compared with control group (FAS: 83.8% *vs*. 64.1%, mean difference: 19.7%, 95%CI: 9.6%~29.4%: PPS: 84.2% *vs*. 64.7%, mean difference: 19.4%, 95%CI: 9.2%~29.1%; both $p < 0.001$) (Fig. 5). Fig. 6 demonstrates the CT manifestations in a patient of the treatment group and the other in the control group.

Treatment with LH capsules was not associated with a higher conversion rate of SARS-CoV-2 viral assay findings (FAS: 76.8% *vs*. 71.1%, mean difference: 5.6%, 95%CI: -4.6%~ 15.7%, $p = 0.279$; PPS: 77.0% *vs*. 71.2%, mean difference: 5.8%, 95%CI: -4.5%~ 15.9%, $p = 0.273$). The rate of conversion to severe cases in the treatment group was similar as compared with the control group (FAS: 2.1% *vs*. 4.2%, mean difference: -2.1%, 95%CI: -7.0%~ 2.4%, $p = 0.498$; PPS: 0% *vs*. 2.2%, mean difference: -1.4%, 95%CI: -76.2%~ 3.1%, $p = 0.247$). Furthermore, there was no significant difference in the median viral assay conversion time between the treatment group and control group (FAS: 11.0 *vs*. 12.0 days, HR: 1.21, 95%CI: 0.92 ~ 1.59; PPS: 11.0 *vs*. 12.0 days, HR = 1.21, 95%CI: 0.92 ~ 1.59; both $p = 0.151$) (Table 2).

Safety

The most common adverse event was the elevated alanine aminotransferase levels or aspartate aminotransferase levels. Other abnormal laboratory testing findings were less common. No overall significant difference in the rate of adverse events was found between the two groups ($p > 0.05$). No serious adverse events were reported (Table 3).

Table 1
Baseline demographic and clinical characteristics.

Variables	Treatment group N = 142	Control group N = 142	*p* value
Age (yr, $\bar{x} \pm s$)	50.4 ± 15.2	51.8 ± 14.8	0.420
Age ≥ 45 yr	89 (62.7%)	102 (71.8%)	0.100
Males (No., %)	79 (55.6%)	71 (50.0%)	0.342
Temperature (℃, $\bar{x} \pm s$)	37.1 ± 0.7	37.09 ± 0.668	0.932
Systolic blood pressure (mmHg, $\bar{x} \pm s$)	128.8 ± 14.4	131.1 ± 15.83	0.203
Diastolic blood pressure (mmHg, $\bar{x} \pm s$)	80.0 ± 10.9	81.2 ± 10.29	0.367
Heart rate (bpm, $\bar{x} \pm s$)	87.5 ± 12.8	85.5 ± 13.58	0.196
Respiratory rate (bpm, $\bar{x} \pm s$)	20.2 ± 2.1	20.7 ± 3.0	0.104
Recent contact with people from Wuhan (No., %)	64 (45.1%)	62 (43.7%)	0.811
Clustered cases (No., %)	27 (19.0%)	28 (19.7%)	0.881
Duration from symptom onset to hospitalization (days, $\bar{x} \pm s$)	9.5 ± 5.1	9.9 ± 5.9	0.591
Symptoms			
Fever (No., %)	71 (50.0%)	77 (54.2%)	0.476
Fatigue (No., %)	75 (52.8%)	69 (48.6%)	0.476
Coughing (No., %)	123 (86.6%)	127 (89.4%)	0.465
Concomitant medications			
Antiviral (No., %)	121 (85.2%)	121 (85.2%)	> 0.999
Antibiotics (No., %)	95 (66.9%)	95 (66.9%)	> 0.999
Immune modulators (No., %)	77 (54.2%)	81 (57.0%)	0.633
Systemic corticosteroids (No., %)	32 (22.5%)	34 (23.9%)	0.779

Discussion

To our knowledge, this is the first multicenter randomized clinical trial that demonstrates the safety and efficacy of LH capsule, a Chinese herb product, in patients with Covid-19. Overall, treatment with LH capsules for 14 days resulted in a significantly higher rate of, and a shorter time to, symptom recovery than control group (usual treatment). The rate of recovery of fever, fatigue and coughing was also higher in treatment group. The rate of conversion of viral RNA assay, however, did not reach to statistical significance. LH capsule had a favorable safety profile for the treatment of Covid-19.

SARS-CoV-2 has been shown to result in an injury of the respiratory tract, nervous system (General Office Of The National Health And Health Commission, 2020), the liver (Chai et al., 2020), the heart, esophagus, kidney, urinary bladder and the jejunum (Li et al., 2020; Zou et al., 2020). The susceptibility of SARS-CoV-2 among the whole population might be related to the ability to potently bind with angiotensin converting enzyme 2 (Zhou et al., 2020). SARS-CoV-2 could infect various cells in human with similar biological behaviors of SARS-CoV (Huang and Herrmann, 2020; Zhou et al., 2020). From the perspective of tissue tropism, the pathological features of Covid-19 mainly resembled those of SARS coronavirus infection (Zhao et al., 2020). In light of the high levels of homology of sequence among SARS-CoV-2, SARS-CoV and Middle East Respiratory Syndrome coronavirus, medications that have been proven to be effective for SARS and MERS might also be adopted to the treatment of Covid-19 (Li and De Clercq, 2020). Unfortunately, no existing antiviral medications are available for the treatment of Covid-19.

Based on a nationwide study with 1099 patients from 552 hospital throughout mainland China, we have recently reported that fever accounted for 88.7% of patients and cough accounted for 67.8% of patients after hospital admission (Guan et al., 2020). In light of the lack of

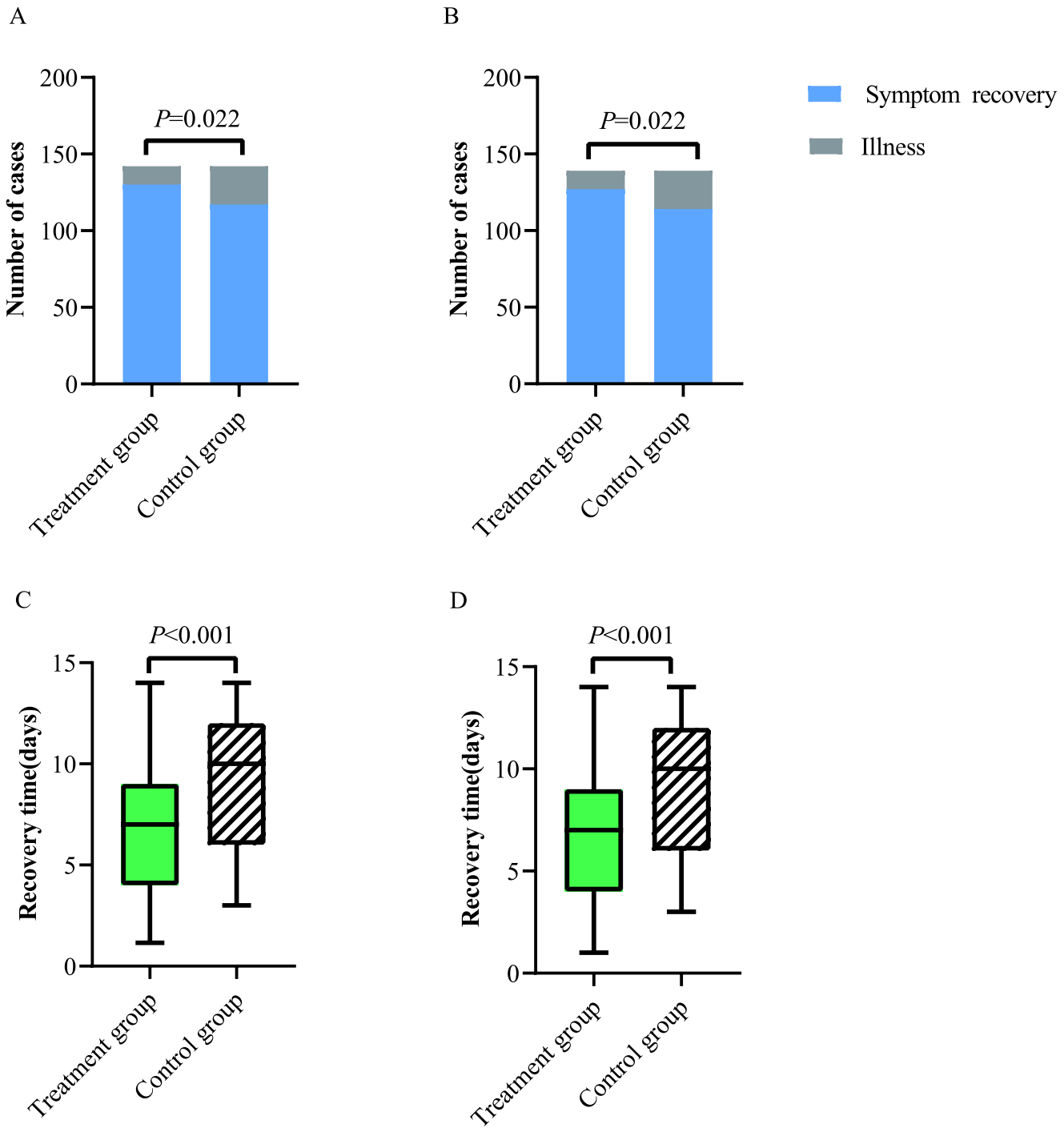

Fig. 2. The rate of and the time to symptom recovery.
Fig. 2-A. Comparison of the rate of symptom recovery in treatment and control group in the full analysis set,
Fig. 2-B. Comparison of the rate of symptom recovery in treatment and control group in the per protocol set,
Fig. 2-C. Comparison of the time to symptom recovery in treatment and control group in the full analysis set,
Fig. 2-D. Comparison of the time to symptom recovery in treatment and control group in the per protocol set,
Shown in the figure are the median value and 95% confidence intervals (95%CI).

validated effective therapeutic approaches, the medications that could ameliorate fever, fatigue and coughing would be valuable for the clinical management of Covid-19. LH capsules, which is a patented product, have been marketed since the outbreak of SARS in 2003 in China. The latest research showed that LH conferred suppression of the cytopathic effect of SARS-CoV-2 *in vitro* and reduced the viral loads in the cytoplasm and cellular membrane (Li et al., 2020). LH could also suppress the replication of SARS-CoV (Zhu et al., 2003), H_3N_2, H_1N_1 and H_7N_9 *in vitro* (Chinese Academy Of Military Hospital, 2009; Ding et al., 2017; Duan et al., 2011; Mo et al., 2007). The inflammatory cytokine storm has been regarded as an excessive host-defense response to the virus (Xu et al., 2020; Zhe Xu, 2020), which can cause diffuse lung injury and predispose to the development of severe disease. Suppression of excessive release of inflammatory meditators is the Holy Grail for halting the progression to severe disease (Xu et al., 2020). Recent studies indicated that LH could dose-dependently inhibit the release of tumor necrosis

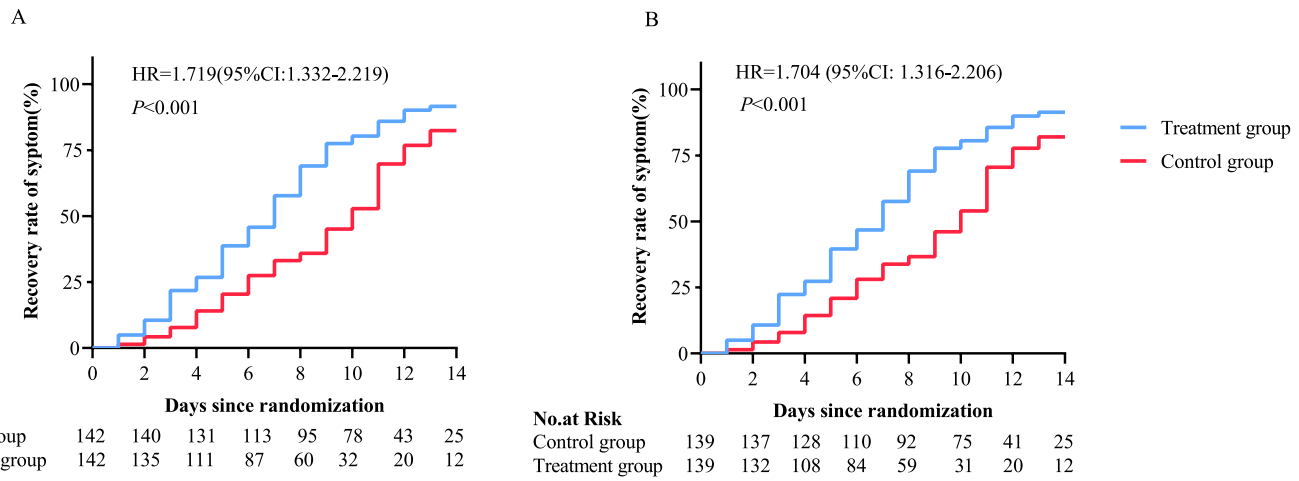

Fig. 3. Dynamic changes in the recovery rate.
Fig. 3-A. Dynamic changes in the recovery rate in the full analysis set,
Fig. 3-B. Dynamic changes in the recovery rate in the per protocol set,
Shown is the Kaplan Meier curve for the rate of recovery of the symptoms (including fever, coughing and fatigue). The percentage of patients who achieved the symptom recovery at individual time points was demonstrated for the control group and treatment group.

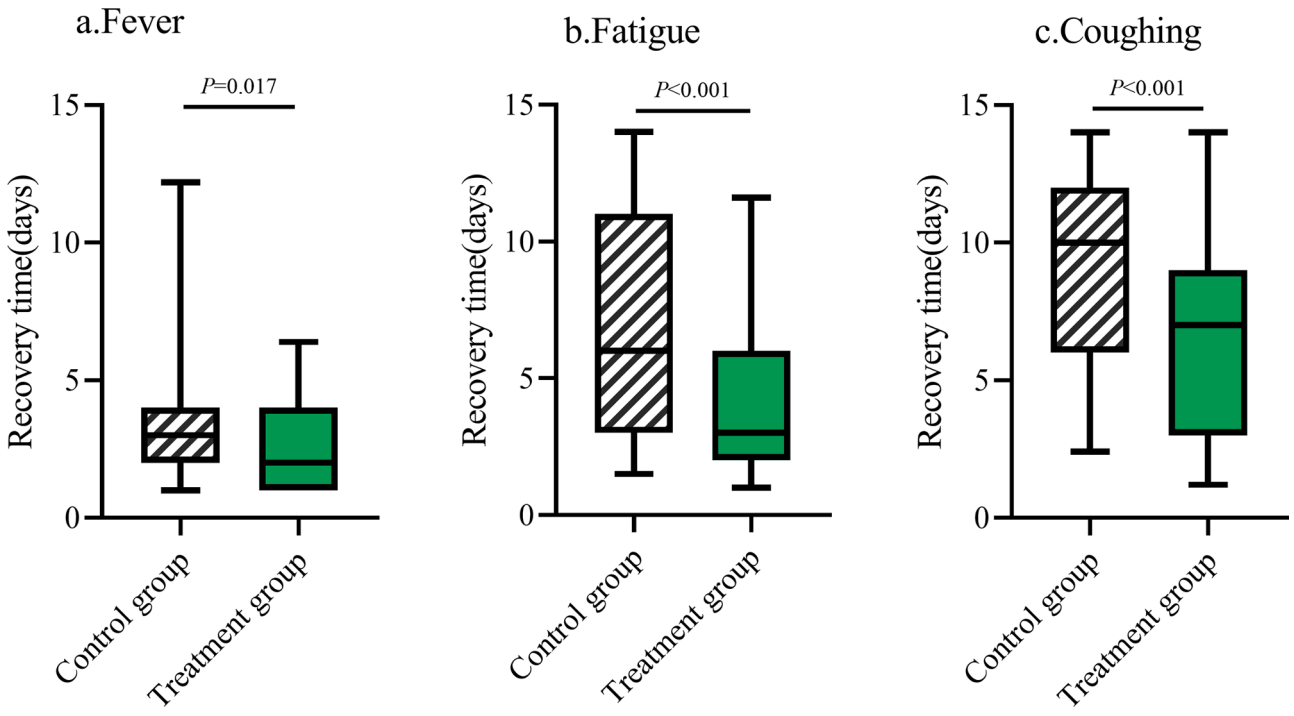

Fig. 4. Time to individual symptom recovery in the full analysis set.

factor-α, interleukin-6, macrophage chemokine protein-1 and induced protein-10 (Li et al., 2020), and could also effectively abrogate the expression of tumor necrosis factor-α, interleukin-6, interleukin-1β, interleukin-2, interleukin-4 and interleukin-13 (Mo et al., 2007), thus ameliorating lung injury associated with inflammatory cell infiltration (Cui et al., 2015). These *in vitro* findings have provided with the rationale for clinical application of LH capsules in Covid-19.

In our study, treatment with LH capsules for 14 days markedly improved the rate of symptom recovery (57.7% at day 5, 80.3% at day 10 and 91.5% at day 14). The time to symptom recovery was also significantly shorter in treatment group. Overall, LH capsules have shortened the duration of fever, fatigue and coughing by 1, 3 and 3 days, respectively. The higher rate of clinical cure and recovery of chest CT manifestations could also be associated with the activity against SARS-CoV-2, and probably, the anti-inflammatory effects. There was a lack of statistical significance for the difference in the rate of, and the time to, conversion of viral assays. These findings differed from those in the *in vitro* studies (Li et al., 2020), possibly because of the difference in the model for observation (human vs. cell models) and the study endpoints (changes in the viral loads in human respiratory tract specimens vs. viral loads in the cytoplasm *in vitro*). No serious adverse events were reported, supporting the safety of LH capsules for the treatment of Covid-19.

LH consists of the key components such as *Lonicera japonica* and *Forsythia suspense* which could block the binding of SARS-CoV-2 with the angiotensin converting enzyme (Niu et al., 2020). *Pogostemon cablin* has been shown to ameliorate diarrhea and improve the host-defense of the

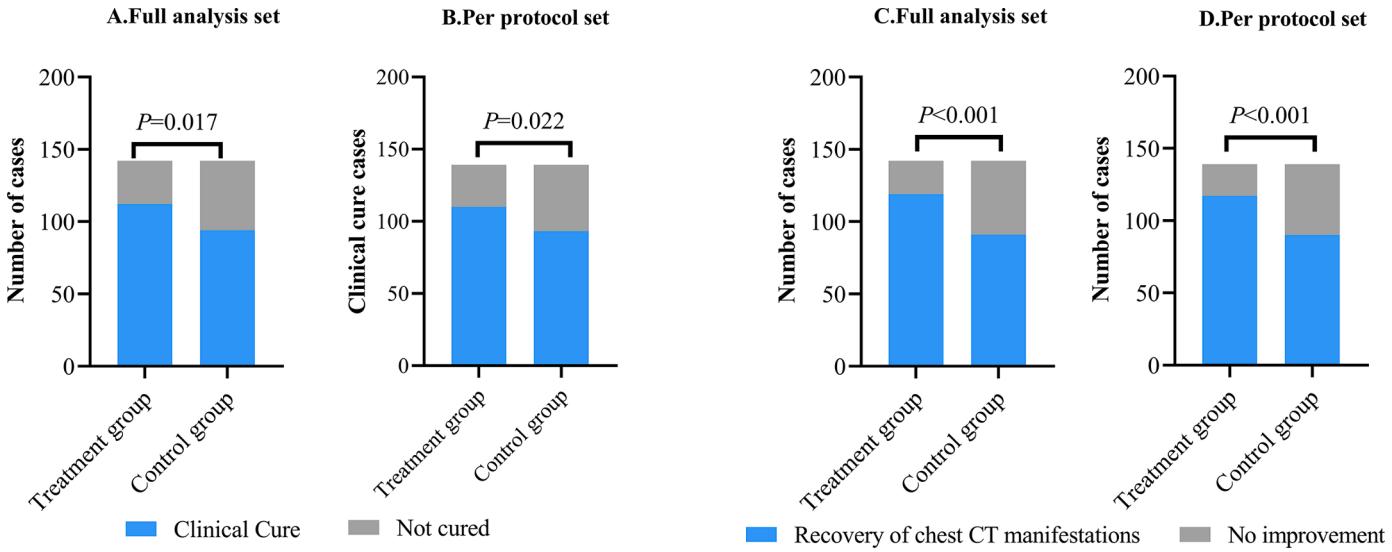

Fig. 5. The rate of clinical cure and the improvement of chest computed tomographic imaging.
We defined the clinical cure as having met all of the following criteria: recovery of body temperature for more than 3 days, symptom recovery, marked improvement in chest CT images, and two consecutive negative SARS-CoV-2 RNA testing (at least one day apart).
An improvement in chest CT images was defined as a decreased area of infiltration, a decreased area of any radiologic abnormality, or decreased density of the ground-glass opacity or nodules.

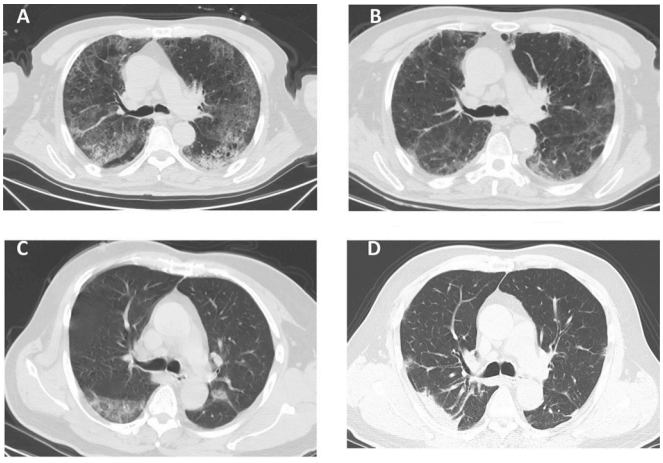

Fig. 6. Chest computed tomographic manifestations at enrolment and after treatment.
Shown are the chest computed tomographic manifestations in a patient of the treatment group and the other in the control group. Panel A: A 71-year-old male who presented with bilateral pulmonary infiltrates at the initiation of treatment with LH capsules; Panel B: Marked absorption of bilateral pulmonary infiltrates at day 12 of the treatment with LH capsules; Panel C: A 66-year-old male who presented with bilateral pulmonary infiltrates (the right lower lobe being more prominent) at the initiation of usual treatment; Panel D: Consolidation of the right lower lobe and absorption of the infiltrations in the left lower lobe at day 10 of the usual treatment.
LH: Lianhuaqingwen

gastrointestinal tract (Zhou, 2018). *Rhodiola rosea* could ameliorate lung injury via the suppression of oxidative stress and apoptosis (HuangFu et al., 2019) and abrogation of pulmonary inflammation (Yao and Luo, 2020). In addition, *Rheum palmatum* could effectively antagonize the binding of spike protein and the angiotensin converting enzyme (Ho et al., 2007) and suppress the excessive release of inflammatory mediators, thus ameliorating the lung injury (Dong et al., 2017). These observations have provided the evidence regarding the antiviral effects of LH capsules.

The exploration of repurposed Chinese herb product would be valuable to the treatment of Covid-19 because, apart from convalescent plasma, no other medications with proven efficacy exist. Our findings indicated that LH capsules could be recommended to patients with Covid-19 for reducing the symptom burden and improving clinical outcomes. However, there are some limitations of the study design. No blinding was implemented because of the urgency of the outbreak that entailed a timely treatment, and placebo-controlled trial would be unethical in light of the rapid outbreak of communicable diseases such as Covid-19. The duration of treatment was established empirically, and whether a prolonged duration would translate into the greater efficacy warrants further investigation. An extended study would be needed to thoroughly explore the effects of LH capsules on the viral shedding and the resolution of all symptoms.

Conclusion

In summary, LH capsules confer therapeutic effects on Covid-19 by improving the recovery rate of symptoms, shortening the time to symptom recovery, and improving the recovery of chest radiologic abnormalities. In light of the efficacy and safety profiles, LH capsules could be considered for the treatment of Covid-19. Future double-blind, prospective, randomized controlled trials are needed to fully evaluate the efficacy of LH capsules in a larger patient population.

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Table 2
Comparison of the primary and secondary endpoints

Variables	Full analysis set Treatment group (N = 142)	Control group (N = 142)	Mean difference 95%CI	HR (95% CI)	Per Protocol set Treatment group (N = 139)	Control group (N = 139)	Mean difference 95%CI	HR (95% CI)
Rate of Recovery at day 14 (n, %)	130 (91.5)	117 (82.4)	9.2 (1.3 - 17.1)		127 (91.4)	114 (82.0)	9.4 (1.3 - 17.4)	
Time to symptom recovery (Median, IQR)	7.0 (6.0 - 8.0)	10.0 (9.0 - 11.0)		1.7 (1.3 - 2.2)	7.0 (6.0 - 8.0)	10.0 (9.0 - 11.0)		1.7 (1.3 - 2.2)
Time to recovery for fever (Median, IQR)	2.0 (1.0 - 2.0)	3.0 (2.0 - 3.0)		1.4 (1.0 - 1.9)	2.0 (1.0 - 2.0)	3.0 (2.0 - 3.0)		1.5 (1.0 - 2.0)
Time to recovery for fatigue (Median, IQR)	3.0 (3.0 - 5.0)	6.0 (4.0 - 8.0)		1.8 (1.3 - 2.5)	3.0 (3.0 - 5.0)	6.0 (4.0 - 7.0)		1.7 (1.2 - 2.5)
Time to recovery for coughing (Median, IQR)	7.0 (5.0 - 7.0)	10.0 (9.0 - 11.0)		1.7 (1.3 - 2.2)	7.0 (5.0 - 8.0)	10.0 (9.0 - 10.0)		1.7 (1.3 - 2.2)
The rate of clinical recovery (n, %)	112 (78.9)	94 (66.2)	12.7 (2.3 - 22.7)		110 (79.1)	93 (66.9)	12.2 (1.8 - 22.3)	
The rate of recovery of chest CT manifestations (n, %)	119 (83.8)	91 (64.1)	19.7 (9.6 - 29.4)		117 (84.2)	90 (64.7)	19.4 (9.2 - 29.1)	
Conversion rate of viral assay	109 (76.8)	101 (71.1)	5.6 (-4.6 - 15.7)		107 (77.0)	99 (71.2)	5.8 (-4.5 - 15.9)	
Time to viral assay conversion	11.0 (8.0 - 12.0)	12.0 (10.0 - 13.0)		1.2 (0.9 - 1. 6)	11.0 (8.0 - 12.0)	12.0 (10.0 - 13.0)		1.2 (0.9 - 1.6)
Rate of conversion of severe cases	3 (2.1)	6 (4.2)	-2.1 (-7.0 -2.4)		3 (2.2)	5 (3.6)	-1.4 (-6.2 - 3.1)	

Table 3
Comparison of the adverse events in the full analysis set

Adverse events	Treatment group	Control group	*p* value
Total	65 (45.8%)	77 (54.2%)	0.154
Abnormal liver function	32(22.5%)	32(22.5%)	1.000
Renal dysfunction	8 (5.6%)	11 (7.7%)	0.476
Headache	1 (0.7%)	1 (0.7%)	1.000
Nausea	6 (4.2%)	5 (3.5%)	0.758
Vomiting	2 (1.4%)	3 (2.1%)	0.652
Diarrhea	8 (5.6%)	19 (13.4%)	0.026
Loss of appetite	8 (5.6%)	6 (4.2%)	0.584

Panel 1
The diagnostic criteria of Covid-19

Item	Criteria
Epidemiology	A recent travel to or residence in Wuhan city or other epidemic regions within 14 days ② Contact with cases from Wuhan city or other epidemic regions or symptomatic cases ③ Clustered cases or having contact with confirmed cases
Clinical manifestation	Fever ② Radiologic characteristics consistent with pneumonia ③ Normal or decreased leukocyte count at early stages, or lymphopenia
Pathogen	Positive findings of RT-PCR assay for viral RNA of respiratory tract or blood specimens ② Detection of SARS-CoV-2 or homology of SARS-CoV-2 in the respiratory tract or blood specimens

Diagnostic criteria: At least one criterion in the epidemiology category, plus any two criteria of the clinical manifestations, plus any criterion for pathogen detection

Author's contribution

Boli Zhang, Lanjuan Li, Yuanlin Song. Zhen-hua Jia and Nan-shan Zhong contributed to study design and quality control, Wei-jie Guan, Zifeng Yang, Jingyi Liang, Zhen-hua Jia and Nan-shan Zhong contributed to the drafting and revision of the manuscript. Ke Hu,Ying Bi, Wei Zhang, Lanjuan Li, Qingquan Liu, Yuanlin Song, Xingwang Li, Zhongping Duan, Qingshan Zheng, Zifeng Yang, Jingyi Liang, Mingfeng Han, Lianguo Ruan, Chaomin Wu and Yunting Zhang contributed to acquisition and the accuracy of the data. Shanghai University of traditional Chinese medicine contributed to statistical analysis. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

CRediT authorship contribution statement

Ke Hu: Data curation, Investigation. **Wei-jie Guan:** Validation, Visualization, Writing - original draft, Writing - review & editing. **Ying Bi:** Data curation, Investigation. **Wei Zhang:** Data curation, Investigation. **Lanjuan Li:** Conceptualization, Data curation, Investigation, Methodology. **Boli Zhang:** Conceptualization, Methodology. **Qingquan Liu:** Data curation, Investigation. **Yuanlin Song:** Conceptualization, Data curation, Investigation, Methodology. **Xingwang Li:** Data curation, Investigation. **Zhongping Duan:** Data curation, Investigation. **Qingshan Zheng:** Data curation, Investigation. **Zifeng Yang:** Data curation, Investigation, Validation, Visualization, Writing - original draft, Writing - review & editing. **Jingyi Liang:** Data curation, Formal analysis, Investigation, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Mingfeng Han:** Data curation, Investigation. **Lianguo Ruan:** Data curation, Investigation. **Chaomin Wu:** Data curation, Investigation. **Yunting Zhang:** Data curation, Investigation. **Zhen-hua Jia:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Nan-shan Zhong:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

None.

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Supplementary materials

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